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Endovascular grafts, stents drive interventional radiology growth

The 21st Annual Scientific Meeting of the Society of Cardiovascular and Interventional Radiology (SCVIR), held in Seattle, Washington, early this month, highlighted important emerging segments of the interventional radiology market, including endovascular grafts for the treatment of aneurysms, dissections, and other vascular defects, as well as vascular stents for the treatment of vascular occlusive disease. Interventional radiology is a rapidly expanding discipline, as evidenced by growth in attendance at the annual SCVIR conference: professional registration increased from 1,474 in 1994 to 2,154 in 1996. That data also underestimates the actual increase in clinicians performing interventional radiology procedures, since both interventional cardiologists and, to a lesser extent, vascular surgeons, are beginning to treat their patients with interventional radiology techniques.

CDU at the Society of Cardiovascular and Interventional Radiology

The trend for multiple disciplines to become involved in this field is indicated by the distribution of sales of percutaneous transluminal angioplasty (PTA) balloon catheters: in 1995, interventional radiologists purchased 71% of the devices, cardiologists purchased 15%, and vascular surgeons purchased 14% of the total units sold in the U.S. Although the entry of other specialists represents a threat to interventional radiologists, for suppliers the trend will expand the market for interventional radiology products, since referral patterns, particularly referrals from vascular surgeons, will diminish as a limiter of expanded use.

Emerging graft and stent applications

Vascular stents are revolutionizing the field of interventional cardiology, and are being used in 30% to 50% of percutaneous coronary revascularization procedures in some centers in the U.S. and Europe. Johnson & Johnson Interventional Systems (Warren, New Jersey), the dominant supplier of coronary stents, achieved estimated sales of $450 million worldwide in 1995, following Food and Drug Administration (FDA) approval of the Palmaz-Schatz coronary stent in August 1994. More than 300,000 Palmaz-Schatz coronary stents have been implanted worldwide since the device was introduced. Stents for peripheral vascular applica-

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AT PRESSTIME: Sonus Pharmaceuticals (Bothell, Washington) has completed patient enrollment in a pivotal Phase III trial of EchoGen Emulsion, an ultrasound contrast agent for use in echocardiography. The trial, which involves 244 patients at 19 clinical sites in the U.S., will complete Sonus's clinical data base for both cardiology and radiology indications for the product in a new drug application. Radiology trials also are under way at five centers in Germany, France, Italy and the United Kingdom.

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tions have been on the market for a considerably longer period of time (the Palmaz stent was approved for iliac artery applications in September 1991), but total implants are less than for the coronary stent due to the lower number of peripheral angioplasty procedures as compared to coronary procedures. However, the use of stents in the peripheral vessels, primarily the iliac and femoral arteries, continues to expand, with **Johnson & Johnson Interventional's** Palmaz stent now being employed in 24% of revascularization procedures for which this device is approved (treatment of common and external iliac artery stenosis, and treatment of common bile duct and hepatic bile duct strictures). **J&J Interventional** will be part of the **Cordis** (Miami Lakes, Florida) unit of **Johnson & Johnson** as the interventional cardiology powerhouse is formed in the wake of the **Cordis** merger into **J&J**.

The Wallstent, manufactured by **Schneider (USA) Inc.** (Minneapolis, Minnesota), a division of **Pfizer Inc.** (New York), is the other stent commonly used in interventional radiology procedures in the U.S. The Wallstent is not yet approved for vascular applications, although approval appears imminent. The device is approved for treatment of malignant biliary strictures and is available for investigational use for transjugular intrahepatic portosystemic shunt (TIPS) procedures.

However, the potential market for peripheral vascular stents may prove to be far larger than current sales would indicate. Potential new applications in the treatment of carotid artery stenosis could expand utilization more than threefold, as indicated in **Table 1**. In addition, the newly emerging area of endovascular stent-grafts promises to open up a related market that may rival the size of the peripheral vascular stent market, with as many as 100,000 patients being potential candidates for the use of endovascular grafts.

Applications of stents in the peripheral vessels include treatment of lesions unsuitable for angioplasty, management of dissection and recoil following angioplasty, and treatment of late angioplasty failures due to restenosis. In addition, a variety of non-vascular applications exist such as treatment of esophageal strictures (the Cook-Z Esophageal stent was just introduced at the SCVIR conference); treatment of biliary and renal strictures, and TIPS.

Table 1
Potential Patient Populations for Applications of Peripheral Vascular Stents and Endovascular Grafts

Disease Category	Number of Patients Requiring Therapy Annually[a]	Patients Treatable With Stents or Endovascular Grafts (Est.)[b]	Applicable Device	Potential U.S. units per year[c]
Femoral/ Iliac Stenosis	140,000	25%-30%	Stent or graft	63,000
Carotid artery	200,000[d]	25%-30%	Stent	90,000
Abdominal aortic aneurysm	44,000	70%	Endovascular graft	30,000
Other aneurysms (thoracic, iliac, other)	37,000	70%	Endovascular graft	26,000
Other vascular stenosis	60,000	25%-30%	Stent	27,000
Trauma-induced arterial lesions	10,000	70%	Stent or graft	10,000
Total	**491,000**			**246,000**

[a] either surgical or interventional procedure
[b] based on either angioplasty restenosis rates, proportion receiving stents/endovascular grafts in clinical studies, or industry estimates
[c] assumes 1.5 stents per procedure for femoral, iliac, carotid and other vessels, and one endovascular graft per procedure
[d] clinicians estimate that less-invasive therapy could be applicable to twice the 100,000+ patients who now undergo carotid endarterectomy

Source: Cardiovascular Device Update

Results with the Palmaz stent in the iliac arteries to date have been suboptimal, according to Dr. Gary Becker of **Baptist Hospital** (Miami, Florida), one of the leading experts in interventional radiology. In addition, a trial employing the Palmaz stent in the femoral arteries (Femoral Artery Stenting Trial, or FAST) was recently halted in part because of issues with compression of the stent as well as due to problems with patient enrollment.

The Palmaz stent lacks longitudinal flexibility, limiting delivery options in the peripheral arteries, and is subject to permanent deformation if compressed. However, iliac artery stenting with the Palmaz stent probably provides improved results as compared to angioplasty alone, since stenting provides an excellent immediate result in many cases that would otherwise be angioplasty failures or lead to suboptimal results, including chronic occlusions, severe dissections, and severe recoil. Other stents under development for use in peripheral vessels are described in **Table 2** on page 3. Many of those

Table 2
Stents and Endovascular Grafts Under Development for Peripheral Vascular Use

Company	Product	Key Features	Status
AngioMed/ C.R. Bard (Karlsruhe, Germany)	Memotherm	Self-expanding nitinol stent with no foreshortening on expansion; ureteral versions available in Europe; versions under development for TIPS, iliac, and biliary applications	IDEs under way for iliac and 510(k) to be filed for biliary applications
Cook Inc. (Bloomington, Indiana)	Fontaine-Dake Stent	Balloon expandable, biocompatible stent with high mechanical flexibility in both compressed and expanded forms: capable of 180-degree bend; intermediate in hoop strength between Palmaz stent and Wallstent	Successful in biocompatibility studies in microswine at 2 months; if successful at 6 months, will proceed to human trials
	Cook-Z Stent	Self-expanding; stainless steel; wire bent in Z-pattern and joined at ends to form a cylinder	Experimental use in iliac arteries in Japan
	Covered Z-Stent (Chuter)	Z-type stents at either end of Dacron graft	In development
	Fontaine-Dake	Tantalum balloon-expandable stent covered with polyurethane or parylene	*In vitro* model studies
Cordis/ Johnson & Johnson (Miami Lakes, Florida)	Cordis Stent	Balloon expandable; tantalum; flexible in undeployed state and rigid in deployed state; 4mm to 12mm deployed diameter; 15mm to 70mm deployed length	Pre-clinical testing complete
	Palmaz Stent	Slotted tube design; balloon-expandable stainless steel stent; shown to inhibit restenosis in coronary vessels	Only stent approved for peripheral vascular applications in U.S.; under evaluation for other applications
	PTFE-covered Palmaz Stent	Both partially covered and fully covered designs under evaluation with inside and outside covering	Pre-clinical studies
InStent Inc. (Eden Prairie, Minnesota)	VasuCoil	Nitinol self-expanding stent; maintains lumen size after flexure; 4mm to 9mm diameter; 40mm length; permanent and temporary versions	About 200 implants worldwide for peripheral applications; preparing IDE filing
Medi-tech/ Boston Scientific (Natick, Massachusetts)	Strecker Stent	Balloon expandable; constructed of interwoven tantalum wire mesh; intermediate flexibility	Preliminary evaluation for peripheral applications in U.S.; widely used in Europe
Medtronic Interventional Vascular (San Diego, California)	Wiktor Stent	Balloon expandable; tantalum; 3mm to 4mm diameter and 15mm length (coronary version); over-the-wire placement	More than 15,000 implanted worldwide (coronary & peripheral); no clinicals for peripheral use in U.S.
Nitinol Medical Technologies/Bard Radiology (Covington, Georgia)	Nitinol Stent	Self-expandable using nitinol thermal memory alloy	Pre-clinical studies
Schneider (USA) (Plymouth, Minnesota)	Wallstent	Self-expanding; stainless steel; 2.5mm to 3.5mm expanded diameter; high longitudinal flexibility; hoop strength somewhat less than Palmaz stent	Awaiting FDA approval for vascular use; approved for treatment of biliary strictures; under evaluation for treatment of colon strictures, maintenance of hemodialysis grafts
SciMed/ Boston Scientific (Minneapolis, Minnesota)	Scimed/ Organogenesis Stent-Graft	Nitinol self-expanding stent with porcine or bovine collagen covering	Animal studies
Corvita Corp. (Miami, Florida)	Corvita Endoluminal Graft	Stainless steel; self-expanding; covering material is interwoven elastomeric polycarbonate urethane fibers, allowing intimal cell migration	In clinical trials in U.S., Europe and Latin America for applications in carotid, AAAs, subclavian, iliac axillary, superficial femoral arteries
Endovascular Technologies (Menlo Park, California)	EndoGraft (Chandbury Hook/Stent)	Dacron graft anchored by proximal and distal hook/stents	Conducting U.S. clinical trials for treatment of abdominal aortic aneurysms under an IDE
Dr. Andrew Cragg MinTec (Freeport, Bahamas)	Cragg Endopro	Self-expanding nitinol wire stent; Dacron and polyester	Clinical studies in Europe
World Medical Manufacturing (Sunrise, Florida)	Talent	Nitinol wire; Dacron and combination Dacron-Teflon stitched covering	Animal studies; clinical studies being organized in Australia

Source: Cardiovascular Device Update

devices already are in use in Europe. However, all have some limitations for peripheral vascular therapy.

Table 2 also describes endovascular grafts under development for the interventional radiology market. At present, most experience with endovascular grafts has been obtained with devices fabricated by clinicians themselves, using existing stents covered with various materials including PTFE (Teflon), Dacron, polyester, silicone, polyurethane, and parylene. However, as demonstrated by Table 2, numerous companies have begun development of endovascular grafts for peripheral vascular applications. A major application of those devices, drawing the focus of most initial development efforts, is the treatment of abdominal aortic aneurysms (AAAs). AAA has an estimated U.S. prevalence of 1.7 million, but only about 190,000 cases are diagnosed each year, including both hospitalized patients and patients treated on an outpatient basis. The National Center for Health Statistics reported 102,000 hospital patients having a diagnosis of AAA in 1993, the latest year for which data is available. Of the total of 190,000 AAA cases, about 44,000 receive surgical treatment. Companies developing endovascular grafts have estimated that 70% of surgical patients may be candidates for alternative endovascular therapy, or about 30,000 patients per year.

Endovascular grafts may also be preferred over stents for therapy of vascular stenosis, if the covering material has a further inhibitory effect on restenosis by blocking cell proliferation in the stent. However, the most recent studies have not indicated that grafts perform better than stents in that application, at least with existing graft designs and materials.

Endovascular grafts may also be employed as an alternative to synthetic grafts used in peripheral vessel reconstruction by vascular surgeons. Corvita Corp. (Miami, Florida), one of the leading developers of endovascular grafts, has estimated that at least 125,000 autologous and 75,000 synthetic grafts are used in peripheral procedures in the U.S., representing another 200,000 potential units per year. Overall, the potential U.S. market for peripheral vascular stents and endovascular grafts may approach 450,000 units per year. While selling prices for endovascular grafts are a subject of conjecture, since none have been introduced to the market, it appears likely that the market could support a price of at least $1,000 per unit given the cost of synthetic grafts of between $300 to over $1,100 each. Average selling prices for peripheral vascular stents are approximately $800 in the U.S., and the Palmaz-Schatz coronary stent is priced at $1,595.

Table 3
Vena Cava Filter Products for Interventional Radiology Applications

Supplier	Product	Key Features	List Price
Bard Radiology/ Nitinol Medical Technologies (Covington, Georgia)	Simon Nitinol Filter	Nitinol construction allows filter to be inserted in collapsed configuration; thermal memory properties provide automatic deployment at body temperature; uses smallest insertion catheter (7Fr-8Fr) of any available device	$935
B. Braun/Vena Tech (Evanston, Illinois)	Vena Tech-LGM	12Fr introducer system; nonmagnetic device; 92%-97% patency; 2% recurrent PE; jugular or femoral approach for placement	$885-$935
Cook Inc. (Bloomington, Indiana)	Bird's Nest	12Fr introducer; stainless steel device; can be placed in vena cavae measuring up to 40mm in diameter; 2.9% occlusion rate; femoral or jugular approach for placement	$850
Medi-tech/ Boston Scientific (Natick, Massachusetts)	Greenfield Filter	12Fr system; stainless steel and titanium versions; 96% patency rate; only percutaneous filter deliverable over a guide wire	$1,126
	Antheor	Biocarbon-coated Phynox alloy material enhances thromboresistance and promotes biocompatibility; 98% patency rate; 98.5% protection against recurrent pulmonary emboli; for vena cava up to 34mm	Not yet approved by FDA
Nehaus Laboratories Inc. (Miami, Florida)	Protect	Infusion catheter with expandable plastic basket surrounding infusion holes to allow trapping of clots for lysis with urokinase; under evaluation for use as a temporary vena cava filter	$500 (approved only for use in thrombolytic procedures)
William Cook Europe (Bjaeverskov, Denmark)	Gunther Filter	Temporary filter with attached catheter allowing removal; for short-term protection against pulmonary embolism in trauma patients and others not requiring permanent implant	Not yet approved by FDA

Source: Cardiovascular Device Update

Use of vena cava filters expands

Vena cava filters have been in use for almost 25 years to prevent pulmonary embolism in patients suffering from deep venous thrombosis (DVT) and other conditions predisposing to thromboembolism. The Greenfield Vena Cava Filter, introduced in 1972 and manufactured by **Medi-tech/Boston Scientific**, is the most widely used device, with more than 150,000 units implanted worldwide as of year-end 1995. **Table 3** describes inferior vena cava (IVC) filter products on the market and under development. Usage of those devices is expanding, as indicated by increases in dollar volume sales of about 35% for the Medi-tech Greenfield filter over the past year in some sales territories.

A number of new IVC filters have been introduced recently or are under development, including the Simon Nitinol filter supplied by **Bard Radiology** (Covington, Georgia); the Antheor filter from **Medi-tech** (not yet available in the U.S.); the Gunther temporary filter under development by **Cook** (Bloomington, Indiana); and the Protect infusion catheter, a device that shows promise for use in temporary protection against pulmonary embolism.

About 2.5 million persons in the U.S. have a significant level of peripheral thrombosis, primarily in the legs, and every year about 600,000 persons suffer pulmonary embolism when clots travel from the thrombosed vessels to the lungs, resulting in about 200,000 deaths annually. The initial mode of therapy to treat that condition and prevent recurrence is anti-thrombotic drugs. However, for patients for whom drug therapy is not feasible (for example, trauma patients who are at risk of hemorrhage), IVC filters are an alternative. IVC filters may be implanted either percutaneously (using a catheter) or surgically. It is estimated that about 25,000 filters were implanted percutaneously in 1995 in the U.S., at an average price of about $1,000, resulting in a U.S. market of about $25 million for percutaneous IVC filters. An estimated 60% of IVC filters are placed percutaneously, with the remaining 40% placed surgically. As a result, the total U.S. market for IVC filters placed by both methods was about $42 million in 1995.

While IVC filters have proven effective in protecting against pulmonary embolism (studies have demonstrated that filters can provide an approximate tenfold reduction in deaths from pulmonary embolism), some complications such as filter occlusion and filter migration can occur, and concerns exist regarding long-term outcome in young patients receiving filter implants. As a result, there have been ongoing attempts to develop temporary removable IVC filters. Devices under development include a temporary version of the Vena Tech filter; the Gunther temporary filter under development by **William Cook** (Europe); and the Protect infusion catheter marketed by **Neuhaus Laboratories** for clot entrapment and lysis, for which an FDA submission for use as a temporary filter is being prepared.

The Gunther temporary filter has been evaluated in a study involving 29 patients conducted over a three and one-half year period ending in January of this year. Filters were implanted for periods ranging from one to 14 days (6.6 days mean), with four patients having filters in place for greater than 10 days. Although no recurrent pulmonary embolism was observed in any of the patients based on clinical symptoms while the filters were in place, complications were observed in 41%. Complications included septicemia, thrombosis of the introduction vein, IVC occlusions (three patients), and, in one case, an inability to remove the filter, resulting in surgical intervention to retrieve the device. Bacteria apparently can colonize the filter via migration up the attached catheter from the percutaneous insertion site in the groin, leading to infections.

Bacterial colonization may also have been partly responsible for the adherence of one filter to the caval wall. The study indicated that the filter can become permanently attached to the caval wall by 12 days following insertion. As a result, the investigators concluded that only a small number of patients would be candidates for use of this device, those having a long life expectancy and clear indications for placement of a filter.

Device prevents distal migration of clots

A second device that has shown some promise in an initial feasibility investigation is the Protect catheter, developed by **Neuhaus Laboratories** (Miami, Florida). The device is approved only for thrombolysis; however, it has the unique feature of an expandable basket formed from the same material used to construct the catheter itself that is intended to capture clots, allowing them to be lysed and preventing distal migration of clots that could result in embolism downstream.

As reported by William J. Miller, MD, of **Riverside Methodist Hospital** (Columbus, Ohio), at the **SCVIR** conference, the Protect catheter has been evaluated in six patients who were at risk for pulmonary embolism but were not able to tolerate thrombolytic drug therapy. The filter was in place for periods ranging from three to 18 days (7.2 average), and no pulmonary embolism occurred in any of the patients. In one case, a clot was observed trapped in the Protect catheter's basket, perhaps indicating that the device was serving to protect against embolism. Although a randomized trial of the Protect will be needed to determine if it can provide significant patient benefit with an acceptable complication rate, this initial study was quite promising. Recent efforts within the managed care environment to mobilize patients as quickly as possible after major surgery have increased the need for temporary IVC filters, Miller said. The Protect already has been used for prevention of pulmonary embolism in Europe.

Additional new products and others under devel-

opment described at the SCVIR conference are expected to expand the utilization of interventional radiology procedures and enhance their effectiveness. Some of the most promising include:

• The Amplatz thrombectomy device, developed by **Microvena Corp.** (White Bear Lake, Minnesota), for use in clearing dialysis fistulae. **Microvena** is awaiting FDA marketing clearance. More than 3,000 Amplatz devices already have been used outside the U.S. Clot-removal efficiency is 92% or greater, with no device-related complications observed in human trials. The device will be priced at $550 for the 50cm version and $900 for the 120cm version, and no capital expenditure is required, as is the case with some other systems now under development.

• The Site-Rite II ultrasound needle guidance system developed by **Dymax Corp.** (Pittsburgh, Pennsylvania), a highly compact, portable, battery-operated ultrasound imaging unit with a hand-held probe used to visualize needle position during venous access procedures at the bedside. List price is $11,000.

• The Clot-Eject Systems thrombectomy catheter, under development by Dr. Gary Gelbfish, MD (New York), which may offer an improved means to remove clots rapidly. The device consists of a 5Fr-7Fr stainless tube with a side window that collects thrombus via suction created with a manual syringe, and a reciprocating cutter to macerate the clot within the tube. The syringe is also used to apply pressure to evacuate the macerated thrombus through a waste channel to avoid clogging. Greater than 98% clot removal has been achieved in animal studies.

• The S.E.T. catheter system developed by **Convergenza** (San Diego, California), a new device for suction-actuated thrombus removal. The over-the-wire device can remove thrombus, using high pressure (1,100 psi) suction in an average of three minutes. A water jet at the tip is used to disrupt the clot. The S.E.T. catheter is not yet approved for marketing in the U.S.

• An endovascular brachytherapy system introduced by **Nucleotron-Oldelft Corp.** (Veenendaal, the Netherlands), under investigation as a means to reduce restenosis following angioplasty or stenting procedures by using radiation to inhibit neointimal cell proliferation. **Nucleotron** is the leading supplier of brachytherapy systems, with 1,150 installations worldwide. Seven hundred of those systems are thought to be suitable for use in endovascular irradiation procedures. Although disposable catheters for brachytherapy represent less than 5% of sales for **Nucleotron**, it is anticipated that endovascular irradiation catheters will sell for prices similar to those for PTA catheters, creating a significant potential for revenue generation for **Nucleotron** if the technology proves efficacious.

New products for the neuroradiology market were introduced by **Target Therapeutics** (Fremont, California) and **Boston Scientific** (Natick, Massachusetts).——

Report from Japan

No synthetics in new vascular graft

Several artificial blood vessel developments have been reported by university and company researchers.

A collaborative group of researchers from the **National Cardiovascular Disease Center** (Osaka) and **Kyoto Prefectural University of Medicine** (Kyoto) has developed a vascular graft that does not use synthetic materials, but instead only protein and cultured tissues. The new graft is characterized by the fact that the host's tissue replaces protein which makes up the graft after the graft has been implanted.

The graft is made by mixing in collagen solution smooth-muscle cells initially harvested from the host, molded into a tube, using a glass tube, and coated with endothelial cells – also initially harvested and cultured from the host.

Experiments made by implanting the graft of 3 cm long and 6 mm inner diameter in a dog's large vein proved that the graft was completely replaced by the host's collagen without any clogging. The merits of the new graft include that it is free from host rejection, and most of all, any length and diameter can be made as required.

A major shortcoming is that it takes approximately three weeks to prepare the graft, so it cannot be used in an emergency situation. Also, the mechanical strength is not sufficient, especially during the period in which the replacement of cells is in progress, requiring reinforcement material such as resin film.

Researchers at **Yokohama City University Medical Faculty** have developed a novel artificial blood vessel that uses water as a sealant. Conventionally, artificial blood vessels are made using polymer material and coating it with collagen or gelatin. The bridging materials, such as glutaraldehyde or formaldehyde used with coating materials, however, are toxic to the body, so safer bridging materials are being sought.

The new graft is based on the properties of fiber, which absorbs a large quantity of water when negatively charged, typically absorbing 700 times to 3,000 times of its weight of neighboring water. A small amount of bovine collagen negatively charged, when coated on the interior surface of teflon grafts available on the market, absorbs a large amount of water within the texture of the graft, filling an entire space within the fiber texture.

Because water particles adsorbed on the surface of the inner wall of the graft electrically repel each other, large particles such as blood cannot penetrate the barrier, while small oxygen particles are allowed to penetrate.

The water particles relay the charge to replace themselves with freshly arriving water particles to maintain the barrier. Water, which acts as a sealant, has no toxicity or antigenecity, eliminating the need for bridging material. The tests made with the graft showed no leakage of blood three weeks after implantation in animals.

Daiichi Pharmaceutical (Tokyo) and **Sumitomo Electric Industries** (Osaka) have jointly developed a vascular graft in which endothelium growth-enhancing substances and anti-thrombotic substances are chemically immobilized. The prototype graft has been successfully tested with dogs for long-term patency.

Using polytetrafluoroethylene (EPTFE) as a substrate, the inner layer of the graft consists of long fiber, while the outer layer consists of short fiber, in order to attain optimum elasticity and pliability. Fibronectin and heparin are chemically bound to the substrate fibers by means of unique hybridization technology the group has developed. Twenty-two patent applications, including one in the U.S. and Canada, have been filed.

Terumo (Tokyo) is developing a vascular graft made of polyester fiber coated with fibrin. A particular type of fibrin is used which attracts vascular cells to form a tissue. A prototype graft 5 mm in diameter and 10 cm long replaced with a dog's vasculature has attained a structure and properties similar to natural blood vessels, with layers of endothelium, smooth muscle and fibroblast. Because the graft is coated by the host's own cells, there will be no rejection reaction and no formation of thrombus. The method allows production of grafts of any diameter and length.

While the vascular graft market in Japan is somewhat stagnant, with annual growth of approximately 5%, a major boost is expected with development of small-diameter grafts applicable to coronary artery replacement. Approximately 10,000 patients are estimated to exist who would benefit from the bypass graft procedure, and with an average of two vessels for replacements, a market of 20,000 vessels potentially exists.

Microscopically observing blood flow

Nihon Kohden (Tokyo) has developed, in collaboration with **Kawasaki Medical School** (Kurashiki, Okayama Prefecture), a technology to directly observe blood flow by microscope. The new device has a needle-like probe equipped with an object lens and a CCD camera, which is connected to a high-speed camera capable of recording 200 images per second. The device allows precision calculation of blood velocity and direction of flow by tracing marker substances such as niobium particles.

While the endomyocardium, which exerts the greatest strength in the heart, was suspected as most prone to creating abnormalities of blood flow, there was no technology available to observe such a state. The new device provides a means to observe and establish a diagnosis, as well as treatment approaches. ———

Business Developments

InControl files IDE for Metrix system

In a pivotal step for its Metrix atrial defibrillation system, **InControl Inc.** (Redmond, Washington) has filed an investigational device exemption application with the Food and Drug Administration to begin U.S. clinical trials of the device.

The request to the FDA came last month, shortly after **InControl** said it had filed with regulatory authorities in Europe to begin clinical trials in up to 12 European centers. The first human implant of the device took place in late October 1995 in London, and the existing and requested trials are designed to lead to receipt later this year of the CE mark allowing market release of the product in Europe. **InControl** has established European headquarters in Brussels, Belgium, to direct the clinical trials and develop a marketing organization.

The Metrix atrial defibrillator is designed to detect the presence of atrial fibrillation, select the proper heartbeat interval, and deliver a low-energy, synchronized shock to convert the fibrillation to normal heart rhythm. It can be placed and programmed by physicians using techniques similar to those used for implanting pacemakers.

Guidant CEO sees window of opportunity

Congressional oversight has led to a speedup in medical device approvals at the Food and Drug Administration (FDA), **Guidant Corp.**'s (Indianapolis, Indiana) top official said at an investors conference. CEO Ronald Dollens said during a session at **Piper Jaffray**'s medical devices conference last month in New York that there had been a recognizable change in attitude at the regulatory agency, but added that there had not yet been a fundamental change, such as would come from legislated reforms.

Dollens said that device companies needed to both take advantage of the attitudinal change to get products approved, and to work for substantive change by pushing for reform legislation. **Guidant** has seen numerous new products emerge from the FDA approval labyrinth in the past several months, including the Ventak Mini implantable defibrillator, which was approved in December.

European companies make acquisitions

Biocompatibles International (London) has acquired **Atlantis Catheter Co.** (Sunnyvale, California) in return for $17.5 million in shares. Atlantis has a pro-

duction site in Galway, Ireland, producing balloon angioplasty products, including guide wires and dilation catheters. Sales in the first nine months of 1995 were just over $600,000, with a pre-tax loss of $888,000 reported. **Atlantis** has not yet obtained FDA manufacturing and product approvals.

Biocompatibles' existing shareholders include **Johnson & Johnson** (New Brunswick, New Jersey), and **Biotechnology Investments** and **3I** (both London). The company has developed improved biocompatibility technology for implants and invasive devices based on phosphorylcholine (PC). The substance was first identified by Professor Dennis Chapman of the **Royal Free Hospital School of Medicine** (London), and is present in the cell membrane of red blood cells in the form of phospholipids. It is the primary natural material responsible for biocompatibility. **Biocompatibles'** first phosphorylcholine-based product was the Proclear soft contact lens, launched in Europe last year. **Biocompatibles** acquired **Lomart Lenses** (Norfolk, Virginia) in September 1994 to provide access to the U.S., almost 50% of the global market.

Biocompatibles has been working with five external contract suppliers to develop a line of PC-coated vascular and non-vascular stents. The acquisition of Atlantis will enable the company to bring development and manufacturing in-house, which should improve control and significantly reduce costs.

Sulzermedica (Winterthur, Switzerland) has acquired two companies controlled by Dr. Peter Osypka, **Osypka GmbH** (Brenzach-Wyhlen, Germany) and its U.S. subsidiary, **Oscor Medical Corp.** (Palm Harbor, Florida). The two companies specialize in several cardiovascular sectors, including pacemaker leads, external pacemakers, high-frequency cardiac ablation using radio frequencies and atrial septum occlusion devices.

The Osypka HAT300, a fifth-generation RF cardiac ablation device widely used in Europe, now has continuous intracardiac ECG recording during the ablation procedure, as well as continuous bioimpedance measurement for verification of tissue contact, and an automatic temperature control. ASDOS is a double umbrella system used for the non-operative occlusion of atrial septum defects. Unusually, complete retraction of the device can be carried out when correct positioning of the umbrellas proves impossible.

Current sales of the two **Osypka** companies are about $21 million. **Sulzermedica's** cardiovascular sales are in excess of $350 million.

Cardiovascular collaboration in China

SmithKline Beecham (Philadelphia, Pennsylvania) is taking several steps to expand its presence in China, especially in a pair of research collaborations centered around the molecular mechanisms of cardiovascular and bone-disorder diseases.

A report in the Feb. 21 issue of *BioWorld Today* indicated that **SmithKline** will support research at the **National Key Laboratory of Medical Genetics** (Changsha, Hunan Province) and at the **Shanghai Second Medical University/Rui Jin Hospital**, and also will establish a training program in which students and research fellows at the institutes will spend time at the company's laboratories in Europe and the U.S. **SmithKline's** business ties with China date to a joint venture formed in 1984. **Tianjin SmithKline French Labs Ltd.** employs more than 600.

Companies . . . in brief

Alexion Pharmaceuticals (New Haven, Connecticut), which is developing C5 inhibitors and apogens designed to treat acute cardiovascular disorders and chronic autoimmune diseases, has conducted an initial public offering of 2.2 million shares at $8.25 a share, which would raise in excess of $18 million . . . **Johnson & Johnson** (New Brunswick, New Jersey) completed its $1.8 billion acquisition of **Cordis Corp.** (Miami Lakes, Florida) in late February . . . **Medtronic Inc.** (Minneapolis, Minnesota) plans to build a $200 million manufacturing plant in Israel to produce pacemaker electrodes . . . **Zoll Medical Corp.** (Burlington, Massachusetts) will make an unspecified payment as part of settling an unfair trade practices and unfair competition suit filed by **Cardiotronics Inc.** (Carlsbad, California) against **Zoll**, with neither company admitting to liability.

Personnel File

❑ **InControl Inc.** (Redmond, Washington) has named W.A. Tacker Jr., MD, PhD, director of research. Tacker joins **InControl** from **Purdue University** (West Lafayette, Indiana), where he has been a professor in the Biomedical Engineering Center and the School of Veterinary Science. He has previously served as a consultant to **InControl**. In another appointment, Gregory M. Ayers, MD, PhD, was promoted to director of clinical research.

❑ **Focal Inc.** (Lexington, Massachusetts), a medical device and drug delivery company that is developing a vascular drug-delivery system to prevent restenosis, has named two persons to key management positions. David Enscore, PhD, was named vice president, development and drug delivery, and Glenn Kazo was named vice president, corporate development. Enscore previously was with **Alza Corp.**, and Kazo was with **Enzon Inc.** and with his own firm, **Kazo Associates.**

Market Updates

Blood-thinning proteins eyed in thrombosis fight

A blood-sucking, iron-depleting, anemia-inflicting nematode bearing the scientific name *Ancylostoma caninum* threatens more than 1 million persons in the Third World – about one in six of the entire world population. Paradoxically, according to a report in *CDU*'s sister publication, *BioWorld Today*, that unwelcome lodger in the bowels of humans and canines secretes proteins that can help prevent a class of diseases that cause approximately half of all deaths in the U.S. Those range from cerebral stroke to pulmonary thrombosis to heart attack and beyond.

In a sense, the body has only itself to blame – not a parasite – for those diverse lethal ailments, all arising from the over-eager action of the life-saving coagulation cascade. Wherever blood is spilled, from a pin-prick to a slashing knife wound to an internal hemorrhage, the bleeding itself signals the coagulation machinery to switch on. The dozen or more blood-clotting factors serially activate one after the other, like the domino effect, with the terminal factor, the enzyme thrombin, forming fibrin. That filamentous protein creates a meshwork, something like sandbags shoring up a flood-threatened levee, to seal off the wound with blood clots.

When the cascade overdoes its wound-healing coagulation by piling on clots (thromboses) which block coronary arteries damaged by atherosclerosis, the result is chronic and fatal cardiovascular diseases. For hookworms to make a living by feeding on human blood, they have to defeat the complex coagulation cascade. They do so by deploying equally subtle blood-thinning inhibitors against specific clotting factors.

Industrial and academic researchers are busy tracking down and cloning those proteins as preventive treatment for the range of devastating thrombotic illnesses.

The March 5 issue of the *Proceedings of the National Academy of Sciences* (PNAS) carried a report by **Corvas International** (San Diego, California) on the anticoagulant repertoire of *Ancylostoma caninum*. Its senior author was George Vlasuk, vice president of biological research at **Corvas**. He and his associates have isolated blood-thinning proteins in particular from *A. caninum*, and created recombinant cDNA clones from three of them, named nematode anticoagulant proteins (NAP), for clinical development.

One of those, NAPc2, is being groomed for Phase I/II clinical trials in the U.S. early in 1997, Vlasuk told *BioWorld Today*. "We've already begun manufacture of clinical supplies for this study, under contract," he said. "And we're starting to put together the necessary documentation to file an investigational new drug application by the end of the year for the Phase I safety study, and take it through to a Phase II efficacy endpoint as well."

An earlier **Corvas** thrombin inhibitor, CVS-1123, a synthetic small molecule, underwent a Phase I clinical trial in the United Kingdom; it ended late last year. Vlasuk said **Corvas** would present some of the data from that study at a scientific meeting in April. "The bottom-line results," he said, "are very positive. The orally delivered drug was well-absorbed in a dose-dependent manner, with no adverse reactions."

The leading anticoagulant drug presently on the market is low-molecular-weight heparin, marketed under the trade name Lovenox by **Rhone-Poulenc Rorer** (Collegeville, Pennsylvania). Heparin is an organic acid derived from slaughterhouse livers and lungs.

Cardiac assist system under development

Researchers at the **Technion** (Haifa, Israel), a research organization affiliated with the **University of Tel Aviv**, are developing a system they say can replace the need for implantable cardiac assist devices and intra-aortal balloon catheters.

The system consists of an electronically controlled vest that surrounds the patient's chest. In the cardiac resuscitation mode, the rate and magnitude of pressure pulses are dictated by the control device; but in the cardiac assist mode, the system senses signals from an electrocardiograph and adjusts its pulse duration and frequency appropriately.

The main applications foreseen will be to provide emergency assistance after a myocardial infarction, after surgery or angioplasty and in the improvement of blood flow to the brain and heart during cardiopulmonary resuscitation. The new system is non-invasive and can be used even by non-specialists.

Ultrafast CT scans effective, study shows

Researchers studying the use of ultrafast computed tomography (CT) scans in detecting deposits that clog coronary arteries have lauded the technique.

As reported in the March 1, 1996, issue of *Circulation*, the journal of the **American Heart Association** (Dallas, Texas), a multicenter study found that the CT scanner accurately detected the presence of calcium deposits in 95% of the 427 patients who proved to have heart disease.

Matthew Buddoff, MD, a cardiologist at **Harbor-UCLA Medical Center** (Torrance, California) who headed the study, said the process was "effective, safe, relatively inexpensive, and very fast." The ultrafast CT scan costs about $400 and takes about five minutes

to complete, Buddoff said. The current standard modality, an exercise ECG taken while a patient jogs on a treadmill, takes five to 12 minutes to complete, costs up to $400, and detects only about 70% of patients with heart disease. Other tests that register higher rates of detection cost anywhere from $600 to $1,200.

While ultrafast CT can be a strong indicator of artery blockage, the researchers cautioned that it should be seen as an initial tool to determine if further tests such as coronary angiography are necessary.

The ultrafast CT scans in the study were performed with scanners made by **Imatron Inc.** (South San Francisco, California). Other major CT scanner manufacturers include **GE Medical Systems** (Waukesha, Wisconsin), **Philips Electronics NV** (Eindhoven, the Netherlands), and **Siemens AG** (Erlangen, Germany).

The study was conducted at **Harbor-UCLA Medical Center**, the **State University of New York at Buffalo**, **Mount Sinai Hospital** (Miami, Florida), the **University of Illinois-Chicago** (Chicago, Illinois), the **University of Iowa** (Iowa City), and **Washington State University Medical Center** (Spokane).

Study cites prognostic indicator

Early resolution of ST segment elevation following an acute myocardial infarction (AMI) is a strong predictor of positive outcome, according to analysis from the INJECT (International Joint Efficacy Comparison of Thrombolytics) trial. The trial, which involved more than 6,000 AMI patients in nine European countries, showed that administration of the thrombolytic agent reteplase, which is under development by **Boehringer Mannheim** (Penzberg, Germany), resulted in increased incidence of early resolution of ST segment evaluation.

A sub-study analysis focusing on 1,398 German patients involved in the INJECT study assessed the results of administration of reteplase in some patients and streptokinase in others. The extent of ST segment elevation resolution was greater in the reteplase group, according to the study.

Dr. Rolf Schroder, one of the researchers, said that administration of reteplase appeared to be a promising, non-invasive early prognostic indicator. He said reteplase-treated patients were indicated as having an increased chance of survival.

Acquisitions & Agreements

❑ **Beckman Instruments** (Fullerton, California) has completed its acquisition of **Hybritech Inc.** (San Diego, California), a subsidiary of **Eli Lilly and Co.** (Indianapolis, Indiana).

❑ **Cardiac Control Corp.** (Palm Coast, Florida) and **Grupo Taper SA** (Madrid, Spain) have signed an agreement for a strategic alliance in Europe and selected countries of the Middle East and Africa, involving distribution by **Grupo Taper** of **Cardiac Control** products beginning with the company's current line of pacemakers. **Grupo Taper** will assist **Cardiac Control** in achieving CE and ISO approvals in Europe, as well as in facilitating relationships with research centers as **Cardiac Control** seeks to expand its single-lead technology.

❑ **Interactive Medical Technologies Inc.** (IMT; Los Angeles, California) has reached an agreement with **E-Z-EM Inc.** (Westbury, New York) under which **E-Z-EM** will begin phase one animal studies of **IMT**'s patented contrast microsphere technology for detection of pulmonary embolism and myocardial ischemia. **IMT** will be the manufacturer of commercialized products that emerge from the trials, while **E-Z-EM** will have licensing rights to those products.

❑ **Opgal Optronic Industries Ltd.** (Tel Aviv, Israel) and **GE Medical Systems** (Waukesha, Wisconsin) have reached an agreement giving **GE Medical** distribution rights to a new line of imaging equipment for cardiac surgeons. The new products, which have not yet been introduced, are designed to help ensure that grafted blood vessels are functioning properly before open-heart surgery is completed. **Opgal** is a joint venture of **Rafael**, the Israeli government's armament development authority, and **Electro-Optics Industries Ltd.**

❑ **Schering-Plough Corp.** (Kenilworth, New Jersey) has elected to pay $1 million to **Corvas International** (San Diego, California) to extend until December of this year its option to expand the research alliance between the companies. The option covers a development program for inhibitors of coagulation Factor Xa, a key enzyme in the blood-clotting process. **Schering-Plough** has paid $14 million to **Corvas** under the alliance to develop new oral drugs for treatment of cardiovascular disorders.

❑ **Texas Biotechnology Corp.** (TBC; Houston, Texas), has signed an additional agreement with **Synthelabo** (Montrouge, France), a subsidiary of **L'Oreal** (Paris) whereby **TBC** will supply data from its Novastan clinical trials in heparin-induced thrombocytopenia/heparin-induced thrombocytopema and thrombosis syndrome (HIT/HITTS) to **Synthelabo**. Novastan (argatroban) is a direct thrombin inhibitor being developed for use in the injectable anticoagulant market. **Synthelabo** will pay **TBC** up to $2.5 million for the patient data from its ongoing trials. **Synthelabo** is developing argatroban in Europe and **TBC** is developing the compound in North America for use with thrombolytics in acute myocardial infarction and as treatment for HIT and HITTS.

Product Pipeline

St. Jude starts trials on X-Cell, Masters valves

Clinical trials on **St. Jude Medical's** (St. Paul, Minnesota) X-Cell stented porcine valve are continuing in Europe, with U.S. trials to begin later in 1996. The X-Cell valve is subjected to an anti-mineralization process to remove potential calcification sites prior to implant.

St. Jude also reported initial U.S. implants of its SJM Masters Series rotatable mechanical heart valve at several U.S. clinical sites, which can be rotated for best valve leaflet position after it is sutured in place. **St. Jude** has received CE mark approval in Europe for the mitral version of the SJM Masters Series rotatable valve.

Elsewhere in the product pipeline:

• **Amersham International** (Little Chalfont, United Kingdom) has received FDA approval for U.S. marketing of its Myoview radiopharmaceutical agent for functional imaging of the heart.

• **Angeion Corp.** (Plymouth, Minnesota) has received an investigational device exemption from the FDA for its radio frequency catheter ablation system, allowing it to set up clinical studies. Up to 20 procedures in up to four centers will be conducted as part of the clinical trial. The RF catheter ablation system is being developed to offer treatment – and possibly a cure – for rapid heartbeats originating in the upper chambers of the heart.

• **Baxter Healthcare Corp.** (Deerfield, Illinois) has received FDA approval to market its Carpentier-Edwards Perimount RSR tissue heart valve, designed to be implanted either inside or on top of the annulus, where the aorta joins the heart.

• **Behring Diagnostics** (San Jose, California), a division of **Hoechst AG** (Frankfurt, Germany), has received FDA approval for U.S. marketing of its cardiac troponin I assay, designed for use with the Opus immunoassays systems as an aide in diagnosing acute myocardial infarction.

• The **Cardiovascular Dynamics** (Irvine, California) subsidiary of **Endosonics Corp.** (Pleasanton, California) has been notified that a U.S. patent will be issued for its low-profile infusion catheter designed to provide greater access to remote locations within the body and precisely deliver therapeutic solutions for coronary, peripheral vascular and neurovascular applications.

• **Ela Medical** (Le-Plessis-Robinson, France), the pacemaker division of **Synthelabo** (Montrouge, France), has placed on general release in Europe and Japan its Opus G single-chamber pacemaker.

• **Immunomedics Inc.** (Morris Plains, New Jersey) has received a U.S. patent for pretargeting methods for detecting and treating cardiovascular, cancerous and infectious lesions.

• **Medlab** (Karlsruhe, Germany) has developed a pulse oximeter board designed for OEM use that requires only 90mW at 5V to operate. The board is smaller than a credit card, and is available with a serial or analog interface and a reusable probe that is easy to clean and sterilize.

• **The Medisol Co.** (Tel Aviv, Israel) has developed a stent system that is flexible during insertion through the artery, but becomes rigid once it is in place. The NIR (new intravascular rigid) flexible stent had its first successful implantation in the heart of a 48-year-old man at **Shaare Zedek Hospital** (Jerusalem). Dr. Yaron Almagor, who performed the operation and who was responsible for the development of the clinical applications, said the new stainless steel stent is a potential boon for use in patients with arteries whose structural problems render the use of conventional stents impossible.

• **Medtronic** (Minneapolis, Minnesota) has launched the Freestyle stentless porcine heart valve in Europe. The aortic root prosthesis is fixed, using alpha-amino-oleic acid instead of the traditional gulatraldehyde-tanning process. **Medtronic** said it will reduce calcification, a long-term problem with many heart valve replacements. **Medtronic's** Hemopump cardiac assist system for ventricular support is on the market in Germany and on a limited basis elsewhere in Europe.

• **Novoste Corp.** (Norcross, Georgia) has started clinical trials of its Beta-Cath catheter system, which is designed to reduce the incidence of restenosis when used immediately following a balloon angioplasty. **Novoste** received an investigational device exemption last fall to conduct the study.

• **Physio-Control Corp.'s** (Redmond, Washington) Lifepak 10C defibrillator/monitor/pacemaker now incorporates the Quick-Combo electrode system, designed to cut costs by using the same electrodes for monitoring, defibrillation, and external pacing.

• **Searle** (Skokie, Illinois) has received FDA approval to market its Covera-HS calcium channel blocker for the treatment of hypertension and angina, with marketing to begin soon. The delivery technology for the drug was developed in conjunction with **Alza Corp.** (Palo Alto, California), which will manufacture the product.

• **Pharmacia & Upjohn Inc.** (London) has said a new study of its blood clot-fighting drug Fragmin in Sweden has shown it cut by 63% the risk of heart attacks among patients with unstable heart disease. ———

The Bottom Line

InStent posts gains in revenues for quarter

InStent Inc. (Eden Prairie, Minnesota) has reported significant increases in revenues in both the fourth quarter and year ended Dec. 31, and lower net losses than in year-earlier periods.

In the fourth quarter, the net loss was $597,000, down from the loss of $649,000 reported a year earlier, on sales of $866,000, up from $266,000.

For the year, the net loss was $1.74 million, less than the loss of $2.37 million in 1994, while sales jumped to $2.4 million from $772,000.

❑ The costs of accelerating the development of **Angeion Corp.**'s (Plymouth, Minnesota) Sentinel implantable cardioverter defibrillator resulted in higher net losses for both the second quarter and six months ended Jan. 31. For the quarter, sales totaled $267,029 compared with no sales in the second quarter of the previous year, while the net loss increased to $2.87 million from $2.24 million a year earlier. For the six months, sales totaled $422,359, again compared with no sales in the year-earlier period, and the net loss increased to $5.58 million from $4.33 million in the comparable period.

❑ Revenues for **Bio-Vascular Inc.** (St. Paul, Minnesota) increased 40% in the first quarter ended Jan. 31, to $2.98 million from $2.12 million in the same year-earlier period. Net income for the maker of specialty medical products for thoracic, cardiac, neuro and vascular surgery was $205,000, compared with a loss of $115,000 in the 1995 first quarter.

❑ **Medical Graphics Corp.** (St. Paul, Minnesota) has reported decreased sales and net losses in both the fourth quarter and six months ended Dec. 31. For the quarter, a net loss of $164,197 was posted, compared with income of $72,029 in the year-earlier period, on sales of $5.7 million, down from $6.4 million in the year-earlier period. For the year, the net loss was $1.73 million, compared with earnings of $657,865 in the previous year, on sales of $21.6 million, down from $23.1 million in 1994.

❑ **Medtronic Inc.** rode what it said were continuing market-share gains in its bradycardia pacing and tachyarrhythmia management businesses to big increases in both revenues and net income in the third quarter and nine months ended Jan. 26. For the quarter, earnings rose nearly 53% to $109.03 million from $71.37 million a year earlier, on sales of $529.2 million, up 28% from the $413.72 million of the year-earlier period. For the nine months, earnings rose 51.5% to $312.4 million from $206.17 million in the comparable period, and sales were $1.57 million, up from $1.22 million the year before.

❑ **Target Therapeutics** (Fremont, California) posted big gains in both earnings and revenues in the third quarter ended Dec. 31, with net income in the quarter rising to $3.62 million from $1.89 million in the comparable period, on revenues of $18.98 million up from $12.47 million a year earlier. The current period included some $1.4 million of initial stocking orders for the Guglielmi Detachable Coil, which was approved by the FDA in the previous quarter. For the nine months, earnings were $8.45 million, up from $5.25 million a year earlier, on sales of $48.62 million, up from $34.49 million.

Next month: Coverage of the American College of Cardiology conference

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